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Caged Glutamates with π-Extended 1,2-Dihydronaphthalene Chromophore: Design, Synthesis, Two-Photon Absorption Property, and Photochemical Reactivity

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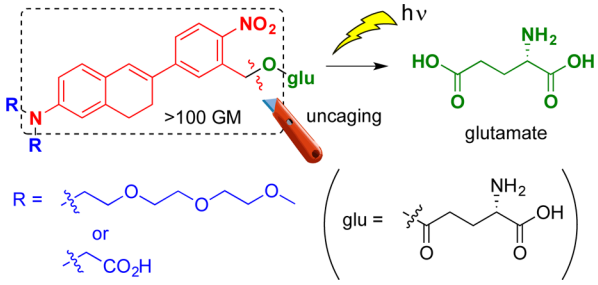

ABSTRACT: Caging and photochemical uncaging of the excitatory neurotransmitter L-glutamate (glu) offers a potentially valuable toolfor understanding the mechanisms of neuronal processes. Designing water-soluble caged glutamates with the appropriate two-photonabsorption property is an attractive strategy to achieve this. Thispaper describes the design, synthesis, and photochemical reactivityof caged glutamates with π-extended 1,2-dihydronaphthalenestructures, which possess a two-photon cross-section of ~120 GMand an excellent buffer solubility (up to 115 mM). High yields up to99% glutamate were observed in the photolysis of two cagedglutamates. Suzuki–Miyaura cross-coupling and Buchwald–Hartwigamination were used as the key reactions to synthesize the caged compounds.

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INTRODUCTION

Caged compounds are important reagents in physiological studies, particularly in the field of neuroscience.[1] Spatially and temporally controlled uncaging of neurotransmitters upon photolysis enables a better understanding of in vivo neuronal processes. For example, caged glutamates play a crucial role when studying mammalian learning and memory mechanisms.[2]

In engineering these probes, several well-defined properties of caged compounds must be considered. A fast and efficient uncaging of the biologically active molecule is important under irradiation conditions, and thermal stability of caged com- pounds is required in the physiological environment. However, affording both significant two-photon absorption (TPA) and good water solubility are among the most recent issues for in vivo studies of caged compounds. Using two photon (near-IR) as opposed to one (UV−vis) allows a deeper penetration depth, reduces scattering in biological tissues, and also reduces optical absorption by endogenous chromophores, causing less photo- damage.[3] Thus, the pertinent molecular design and synthesis of new caged compounds, based on chromophores with a high TPA cross-section (σ_2 in GM), remains a challenge.

In the last two decades, several types of caged glutamates such as nitrobenzyl-, 7-aminocoumarinyl-, ruthenium biphenyl-, and carboxymethylnitroindolinyl-caged compounds have been designed and synthesized for physiological studies (Figure 1). Examples (including their reported two-photon uncaging cross sections, $\sigma_2\Phi_u$)[4] include N-nitrophenethyloxycarbonyl (Noc- glu),[5] carboxynitrobenzyl (CNB-glu),[6] bromohydroxycoumarin (Bhc-glu, 1 GM[7]/740 nm),[8] methoxynitroindolinyl (MNI-glu, 0.06 GM/740 nm),[9] carboxymethylnitroindolinyl (CDNI-glu, 0.06 GM/720 nm),[10] propylmethoxynitrobiphenyl (PMNB-glu, 0.45 GM/800 nm),[11] ruthenium bipyridine (RuBi, 0.14 GM/ 800 nm),[12] and bisnitropropylstyrylfluorene (BNSF-glu, 5 GM/800 nm).[13] Recently, we reported the synthesis and photochemical reactivity of caged glutamates with a π-extended coumarin chromophore (HBC-glu) as a photolabile protecting group.[14]

Herein, we report the design, synthesis, and TPA properties of caged glutamates 4 and 5 with a rigid stilbene-based structure (see Figure 3). Their photochemical release of glutamate was assessed in this study.

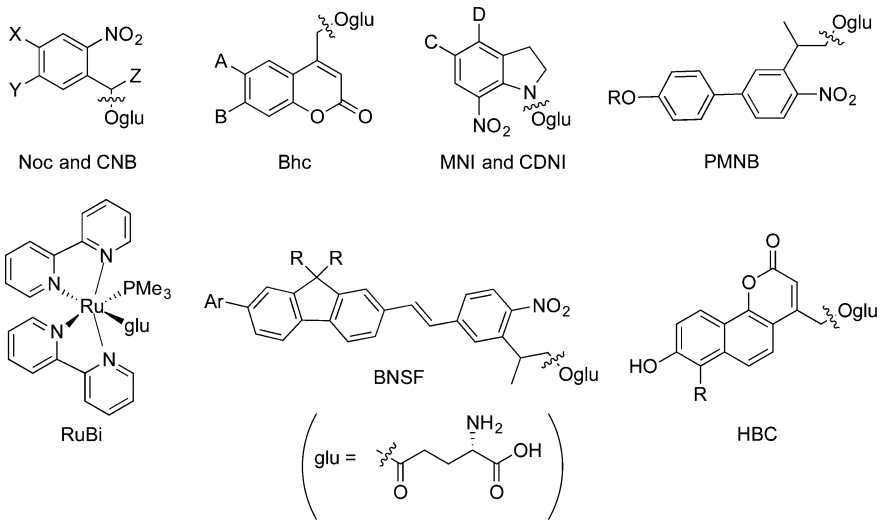
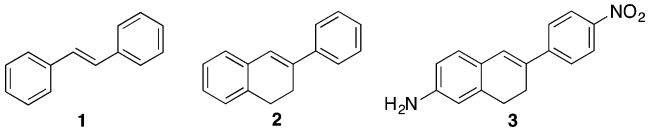


Figure 1. Examples of caged glutamates.

RESULTS AND DISCUSSION

Molecular Design of High TPA Chromophore with Uncaging Reactivity. Extended π-conjugated molecules, such as stilbene derivatives, are promising candidates for chromophores with high TPA responses.[15,16] According to the literature, E-stilbene 1 has a TPA cross-section of 12 GM at 514 nm.[17] The corresponding computed value at the INDO-MRD-CI level at 27.3 GM at 466 nm has the same order of magnitude.[16] The major reactivity of the electronically excited state of stilbenes, i.e., the deactivation process, is the cis–trans isomerization reaction. However, the bond-cleavage reaction from the electronically excited state is indispensable for the uncaging of biologically active compounds upon photolysis. Thus, the simple ring-closed 1,2-dihydronaphthalene structures 2 and 3 were selected to avoid any cis–trans isomerization in the electronically excited state. The nitro group is needed for the uncaging process and the amino group for water solubility. This also adds a push–pull character to the chromophores that is well-known to favor increased TPA responses.[3k]



Initially, the one-photon absorption (OPA) and TPA spectra of parent chromophore units 2 and 3, with a 1,2- dihydronaphthalene core, were computed at the TD-B3LYP/ 6-31G(d)//HF/6-31G(d) theory level in a vacuum (Figure 2). This level of theory has been shown to provide accurate predictions for structure–TPA relationships.[3k] Both chromophores led to sizable TPA cross sections (σ_2) of ~150 GM, however, in different spectral regions (Figure 2; and see the Supporting Information for details). In fact, compound 2 had its first TPA maximum at 470 nm, strongly blue-shifted to two times the wavelength of its first OPA maximum (Figure 2a). As expected, due to the push–pull character introduced by the nitro and amino groups, the first TPA maximum of compound 3 was

significantly red-shifted relative to compound 2, with a good agreement between OPA and TPA maxima.[3k] The computed TPA spectrum of 3, with a sizable TPA cross-section (σ_2) from 600 to 900 nm, prompted us to synthesize the caged glutamates 4 and 5, and investigate their photochemical reactivity (Figure 3).

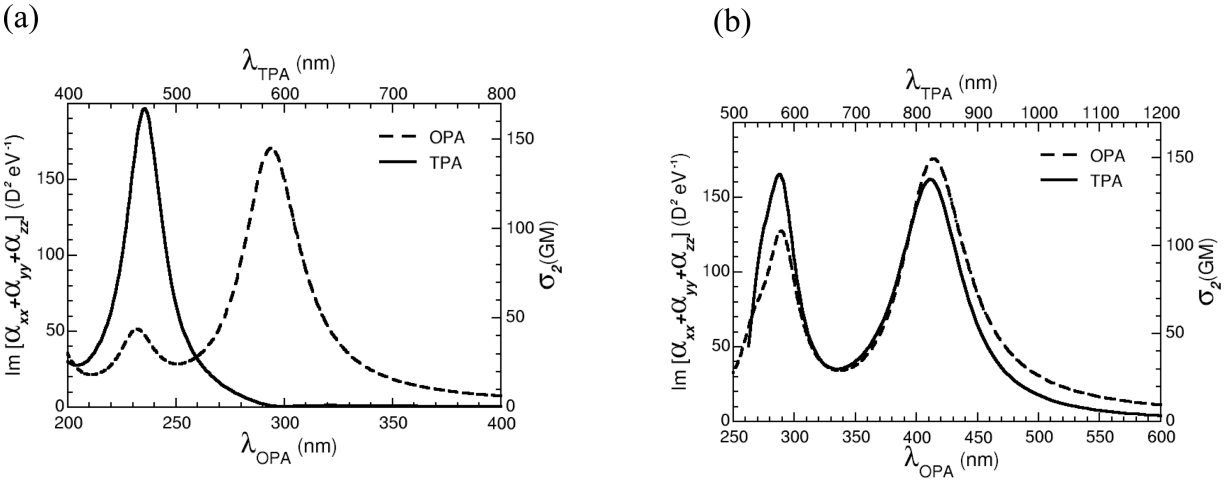


Figure 2. Calculated OPA (dashed lines) and TPA (solid lines) spectra of (a) compound 2 and (b) compound 3 in a vacuum at the TD-B3LYP/6- 31G(d)//HF/6-31G(d) theory level.

Synthesis of Caged Glutamates 4 and 5. Fundamen- tally, compounds 4 and 5 consisted of three units, which included the photolabile protecting group unit (Unit-1) with an o-nitrophenyl structure and rigid stilbene TPA chromophore; amino groups (Unit-2) with hydrophilic groups, which were an indispensable water solubility unit; and the neurotransmitter glutamic acid (Unit-3). The strategy for the syntheses of caged glutamates 4 and 5 with a rigid stilbene structure is summarized in Figure 3.

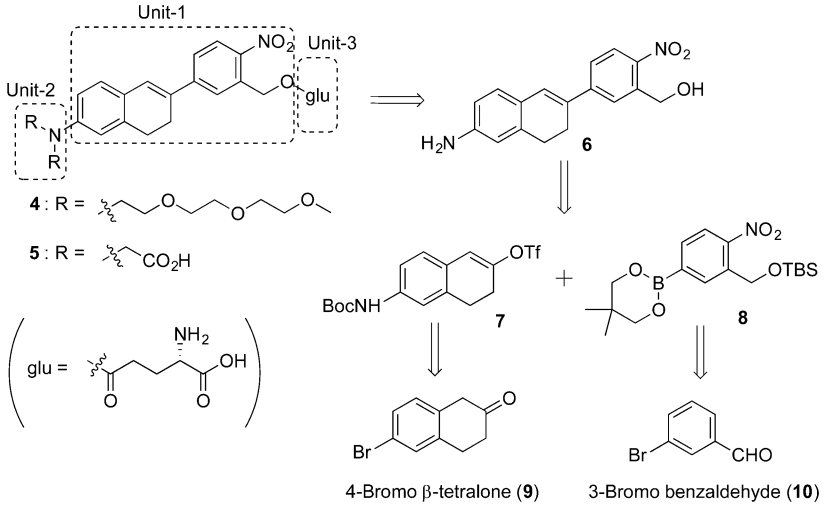
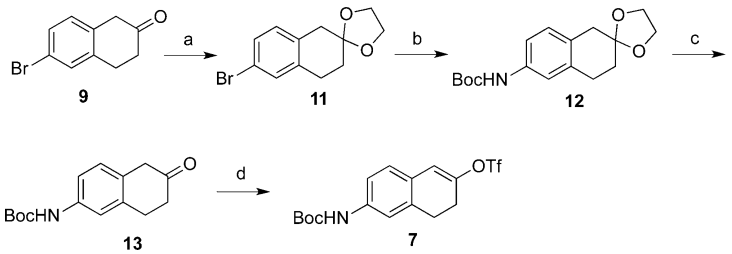


Figure 3. Retrosynthesis of caged glutamates 4 and 5 with a rigid stilbene structure.

Caged compounds 4 and 5 were synthesized from a common intermediate 6 by base-

mediated bis N-alkylation and the introduction of a glutamate moiety by condensation with the hydroxy terminal. It was anticipated that a Suzuki–Miyaura cross-coupling of enolic triflate 7 with aryl boronate 8 would allow the preparation of the key intermediate 6. Fragments 7 and 8 were obtained from the known 4-bromo-2-tetralone (9) and the commercially available 3-bromobenzaldehyde (10), respectively.

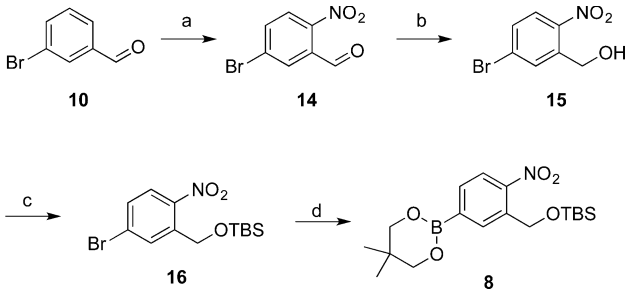
Scheme 1[a]



[a]Reagents and conditions: (a) ethylene glycol, p-TSA·H_2O, C_6H_6, reflux, Dean Stark, 6 h, 95%; (b) tert-butyl carbamate, Cs_2CO_3, $Pd_2(dba)_3$, xanthphos, dioxane, 100 °C, 24 h, 85%; (c) p-TSA·H_2O, acetone, rt, 3 h, 80%; (d) $PhNTf_2$, NaHMDS, THF, –78 °C, 0.5 h, 75%.

The enolic triflate fragment 7 was synthesized in four steps, starting with 4-bromo-2-tetralone 9[18] (Scheme 1). Ketone protection using ethylene glycol in the presence of catalytic p- toluenesulfonic acid (p-TSA) monohydrate afforded 11 in a 95% yield. The Buchwald amination reaction with tert-butyl carbamate provided 12 in a 85% yield.[19] Deprotection of the ethylene ketal moiety was achieved by catalytic usage of p-TSA to furnish 13 in a 80% yield. Ketone 13 was finally converted to the desired enolic triflate 7 using phenyl trifluoromethane sulfonamide ($PhNTf_2$) in a 75% yield.

Scheme 2[a]



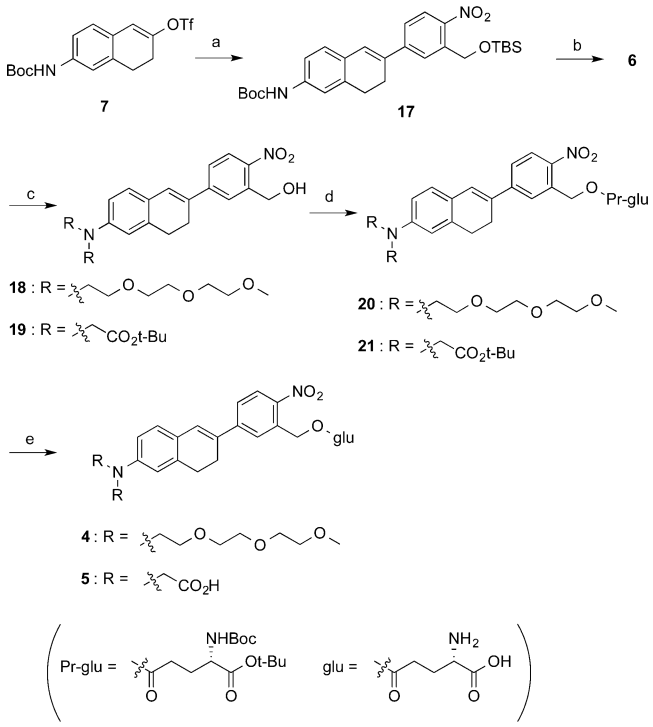
[a]Reagents and conditions: (a) KNO_3, H_2SO_4, 0 °C to rt, 1 h, 70%; (b) $NaBH_4$, MeOH, 0 °C to rt, 15 min, quantitative; (c) TBS-Cl, imidazole, CH_2Cl_2, 0 °C to rt, 12 h, 90%; (d) bis(neopentyl glycolato) diboron, $PdCl_2$(dppf), CH_3COOK, CH_3CN, 100 °C, 1 h, 90%.

Another fragment, aryl boronate 8, was synthesized from commercially available 3-bromo benzaldehyde (Scheme 2). The aldehyde 10 was subjected to nitration to provide 14 in a 70% yield, followed by rapid reduction with $NaBH_4$ to furnish the primary alcohol 15 in a quantitative yield. The primary alcohol was protected using tert-butyl dimethylsilyl chloride (TBS-Cl) and imidazole to produce silyl ether 16 in a 90% yield. Compound 16 was converted to boronate 8 in a 90% yield using bis(neopentyl glycolato)diboron.

With both enolic triflate 7 and aryl boronate 8 fragments, we coupled the fragments to

generate the key intermediate 6 (Scheme 3). Accordingly, subjection of enolic triflate 7 to Suzuki–Miyaura cross-coupling[20] with aryl boronate ester 8 afforded the required skeleton of chromophore 17 in a 85% yield. The deprotection of both the silyl and tert-butylox- ycarbonyl (Boc) groups was performed using trifluoroacetic acid, resulting in amino alcohol 6 in a 95% yield.

Scheme 3[a]



[a]Reagents and conditions: (a) 8, $PdCl_2(dppf)$, NEt_3, THF/H_2O (9:1), reflux, 1 h, 85%; (b) TFA, CH_2Cl_2, 0 °C to rt, 1 h, 95%; (c) 1-bromo- 2-(2-(2-methoxyethoxy)ethoxy)ethane or bromo tert-butyl acetate, triisopropylamine, NaI, acetonitrile, reflux, 24 h, 75% for 18 or 80% for 19; (d) ((S)-5-tert-butoxy-4-(tert-butoxycarbonylamino)-5-oxopenta- noic acid) (22), EDC, DMAP, CH_2Cl_2, rt, 24 h, 90% for 20 or 80% for 21; (e) TFA, CH_2Cl_2, rt, 5 h, quantitative.

At this stage, water-soluble groups, necessary for biological study, were introduced at the nitrogen terminal. First, treatment of 6 with 1-bromo-2-(2-(2-methoxyethoxy)ethoxy)ethane and α-bromo tert-butylacetate in the presence of an N-ethyl- diisopropylamine base in acetonitrile produced the bis-alkylated products 18 and 19 in 75% and 80% yields, respectively. Finally, the protected glutamic acid Pr-glu ((S)-5-tert-butoxy-4- (tert-butoxycarbonylamino)-5-oxopentanoic acid,[21] 22) was introduced to cages 18 and 19 to provide glutamate analogues 20 (λ_{max} 443 nm in MeOH, ε 29520 M^{-1} cm^{-1}) and 21 (λ_{max} 420 nm in MeOH, ε 18377 M^{-1} cm^{-1}) in 90% and 80% yields, respectively. The deprotection of trifluoroacetic acid provided caged glutamates 4 and 5 as TFA salts in quantitative yields. The solubility of 4 and 5 in a HEPES buffer at pH 7.4 was 115 and 35 mM, respectively, at room temperature. Both 4 and 5 were thermally stable in a HEPES buffer up to 100 °C.

Photochemical Reactivity of Compounds 20 and 21. The photochemical release of protected glutamic acid 22 from compounds 20 and 21 was investigated by the irradiation of samples (around 10 mM in CD_3OD) using a YAG laser at 355 nm (~7 mJ/pulse) (Figures 4 and 5). The photochemical reaction was monitored using ^1H NMR (400 MHz)

spectroscopic analysis. As shown in Figures 4 and 5, quantitative uncaging of the glutamate unit 22 was proven by comparing the ^{1}H NMR spectrum (Figures 4c and 5c) with the authentic sample of 22 (Figures 4d and 5d). The chemical yield of compound 22 after 20 h irradiation was >95% for compound 20 and after 24 h irradiation was >99% for compound 21, using Ph_3CH as an internal standard in both cases. The quantum yield for the formation of protected glutamic acid 22 from glutamate analogues 20 ($\varepsilon_{355} = 5961$) and 21 ($\varepsilon_{355} = 5740$) was ~0.01 at 355 nm irradiation using Nd:YAG laser (10 Hz, ~7 mJ, 4–5 ns pulse-width). The photochemical formation of acetophenone ($\Phi = 0.33$) from valerophenone was used as a chemical actinometer reaction.[22] Thus, the $\varepsilon_{355}\Phi$ value was calculated as 59.6 and 57.6 for 20 and 21, respectively.

Synthesis of Parent Compound 23 and Its TPA Spectrum. The photochemically stable compound 23 was synthesized to measure the TPA spectrum (Scheme 4). Enolic triflate 7 was coupled with 4-nitrophenylboronic acid through a Suzuki–Miyaura reaction, using $Pd(PPh_3)_4$ and Cs_2CO_3 and cesium carbonate as a base, leading to the parent core skeleton 23 in a 91% yield.

The TPA spectrum of the rigid stilbene chromophore 23 (11.7 mM) is shown in Figure 6b, together with the OPA spectrum (Figure 6a) in chloroform. The TPA spectrum was measured by nondegenerated absorption between the 800 nm pump and white light probe beam. A multichannel lock-in amplifier was used for data collection, which provided fine resolution and high signal-to-noise ratio. A TPA value of ~120 GM was observed at 680 nm.

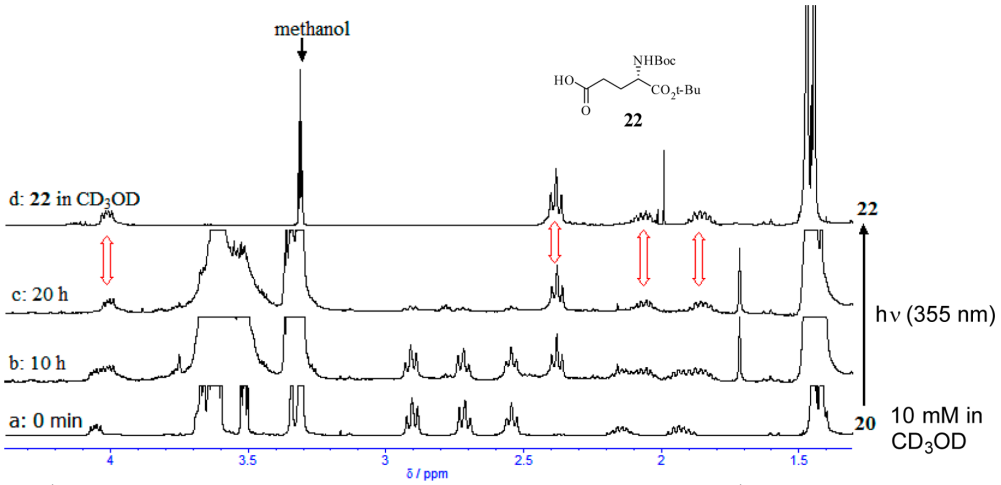


Figure 4. (a) ^{1}H NMR (400 MHz) of compound 20 in CD_3OD; (b) ^{1}H NMR spectrum (δ 1.4–4.4 ppm) after 10 h irradiation of 20 using YAG laser (355 nm) in CD_3OD; (c) ^{1}H NMR spectrum after 20 h irradiation of 20 in CD_3OD; (d) ^{1}H NMR spectrum of protected glutamic acid 22 in CD_3OD.

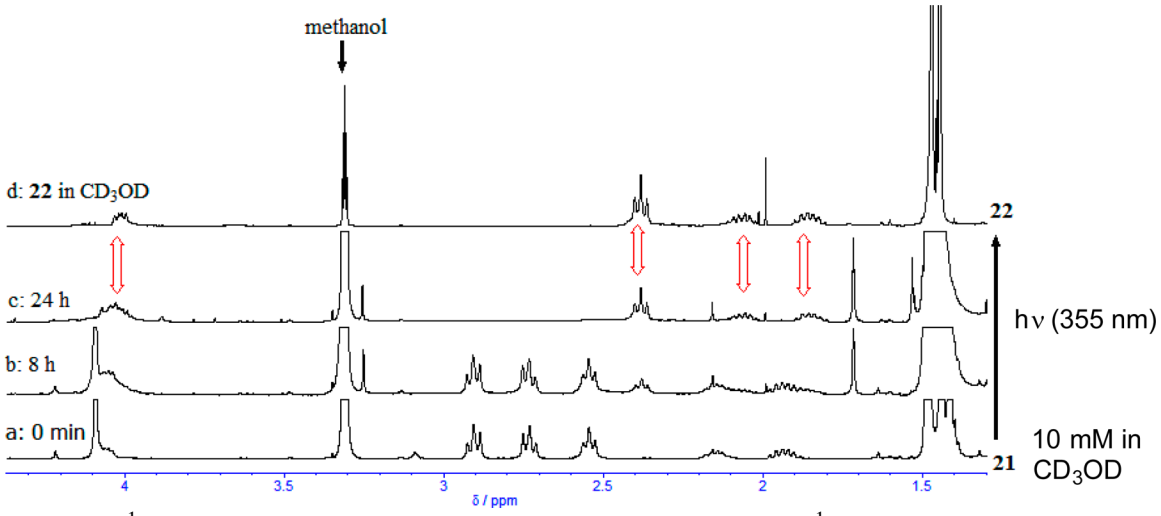
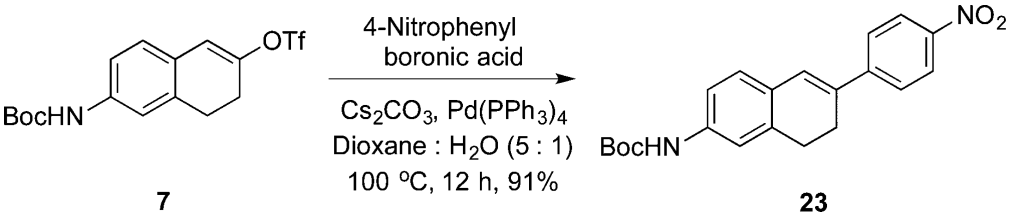


Figure 5. (a) ^{1}H NMR (400 MHz) of compound 21 in CD_3OD; (b) ^{1}H NMR spectrum (δ 1.4–4.4 ppm) after 8 h irradiation of 21 using YAG laser (355 nm) in CD_3OD; (c) ^{1}H NMR spectrum after 24 h irradiation of 21 in CD_3OD; (d) ^{1}H NMR spectrum of protected glutamic acid 22 in CD_3OD.

Scheme 4. Synthesis of Compound 23 for Measuring the TPA Spectrum



7 **23**

(a) (b)

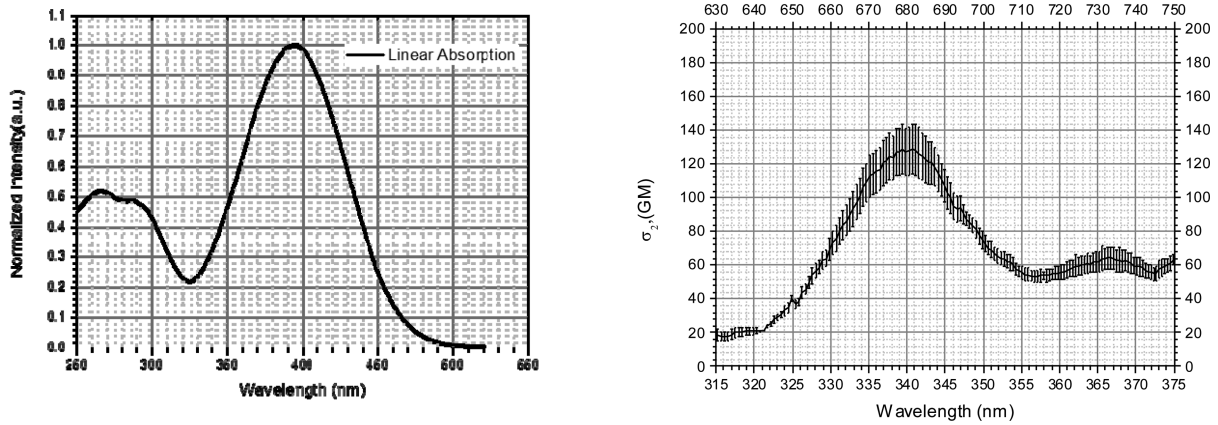


Figure 6. (a) OPA spectra of compound 23, λ 250–550 nm. (b) TPA spectra of compound 23, λ 630–750 nm.

SUMMARY

In summary, this study designed and synthesized two new caged glutamates with π-extended 1,2-dihydronaphthalene chromophore. The synthetic sequence was highly convergent with an overall yield of approximately 28%. These two caged glutamates 4 and 5 showed excellent buffer solubility (up to 115 mM), with the photochemical reaction shown to release glutamic acids in high yields (>95%). A TPA value of ~120 GM at 680 nm was obtained for the parent structure 23. Further elaboration of this sequence for more efficient caged glutamates is currently underway in our laboratory.

EXPERIMENTAL SECTION

Commercially available reagents and solvents for syntheses were reagent grade and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with an NMR spectrometer. $CDCl_3$ (0.03% TMS) was used as deuterated solvents. Chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane, and the coupling constants (J) was reported in Hertz (Hz). While the HRMS spectra was recorded on a Orbitrap XL instrument using the positive ion mode.

The synthetic procedures for new compounds prepared in this study follow.

6′-Bromo-3′,4′-dihydro-1′H-spiro[[1,3]dioxolane-2,2′-naph- thalene] (11). 6-Bromo-3,4-dihydronaphthalen-2(1H)-one (9) (4.5 g, 20.1 mmol) was dissolved in benzene (50 mL), to which ethylene glycol (2.27 mL, 40.2 mmol) and p-TSA·H_2O (191 mg, 1.0 mmol) were added. The solution was heated under reflux conditions with a Dean−Stark trap attached for 6 h. The reaction mixture was cooled and washed with saturated aq $NaHCO_3$ (20 mL) and water (20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Crude was purified by flash silica gel column chromatography (15% ethyl acetate in hexanes) to give required compound 11 (5.2 g, 95%): IR (neat) ν 2951, 2881, 1591, 1484, 1104, 1062, 859, 803, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.23 (dd, J = 8.5, 2.1 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 4.04− 4.00 (m, 4H), 2.95 (t, J = 6.9 Hz, 2H), 2.92 (s, 2H), 1.93 (t, J = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 133.4, 131.2, 130.7, 128.8, 119.6, 107.8, 64.5, 38.7, 31.4, 27.8; HRMS-APCI calcd for $C_{12}H_{14}O_2Br$ 269.0171, found 269.0172 $[M + H]^+$.

tert-Butyl (3′,4′-Dihydro-1′H-spiro[[1,3]dioxolane-2,2′-naph- thalen]-6′-yl)carbamate (12). 6′-Bromo-3′,4′-dihydro-1′H-spiro- [[1,3]dioxolane-2,2′-naphthalene] (3.7 g, 13.7 mmol), tert-butyl carbamate 11 (1.93 g, 16.5 mmol), cesium carbonate (6.72 g, 20.6 mmol), $Pd_2(dba)_3$ (125 mg, 0.13 mmol), and xanthphos (238 mg, 0.41 mmol) in anhydrous dioxane (20 mL) were heated at 100 °C under nitrogen atmosphere for 5 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (50 mL), filtered, and concentrated in vacuo. The crude was purified by flash silica gel column chromatography (20% ethyl acetate in hexanes) to give the required compound 12 (3.56 g, 85%): mp 144−145 °C; IR (neat) ν 3337, 2977, 1724, 1532, 1366, 1243, 1058, 882, 814 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (s, 1H), 7.02 (dd, J = 7.8, 2.1 Hz,

1H), 6.94 (d, J = 7.8 Hz, 1H), 6.46 (s, 1H), 4.03–3.99 (m, 4H), 2.94 (t, J = 6.9 Hz, 2H), 2.92 (s, 2H), 1.92 (t, J = 6.7 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 136.3, 135.9, 129.5, 129.1, 118.3, 116.6, 108.3, 80.2, 64.4, 38.5, 31.7, 28.3, 28.1; HRMS-ESI calcd for $C_{17}H_{23}O_4NNa$ 328.1519, found 328.1524 $[M + Na]^+$.

6-((tert-Butoxycarbonyl)amino)-3,4-dihydronaphthalen-2-yl Trifluoromethanesulfonate (7). To the stirred solution of tert-butyl (3′,4′-dihydro-1′H-spiro[[1,3]dioxolane-2,2′-naphthalen]-6′-yl)-carbamate (12) (3 g, 9.83 mmol) in acetone (30 mL) was added p- TSA·H_2O (186 mg, 0.97 mmol). Stirring was continued for 3 h at room temperature. After completion of reaction, the reaction mixture was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (10 mL). The reaction mixture was evaporated at reduced pressure, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, evaporated under reduced pressure, and purified through silica gel column chromatography (20% ethyl acetate in hexanes) to give required compound 13 (2 g, 80%). The product was not stable, so it was used immediately in the next step.

tert-Butyl (6-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)carbamate (13) (750 mg, 2.87 mmol) and N-phenylbis(trifluoromethanesulfonimide) (1.33 g, 3.7 mmol) were dissolved in anhydrous THF (30 mL), and the mixture was cooled to −78 °C under nitrogen atmosphere. To this solution sodium bis(trimethylsilyl)amide (0.6 M solution in toluene, 9.5 mL, 5.74 mmol) was added dropwise via syringe at −78 °C slowly dropwise (color changes to orange). The mixture was stirred at −78 °C for an additional 30 min (monitored by TLC) before the reaction was quenched by addition of distilled water. The reaction mixture was then extracted with Et_2O (3 × 10 mL), washed with brine (20 mL), dried over Na_2SO_4, and filtered, and the solvent was evaporated in vacuo. Purification by flash silica gel column chromatography (10% ethyl acetate in hexanes) afforded required compound 7 (1.12 g, 75%): mp 80–82 °C; IR (neat) ν 3318, 2995, 1693, 1580, 1522, 1240, 1141, 1061, 886, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.06 (dd, J = 8.2, 2.2 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.50 (s, 1H), 6.42 (s, 1H), 3.02 (t, J = 8.5 Hz, 2H), 2.66 (t, J = 8.5 Hz, 2H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 148.7, 138.5, 134.1, 127.8, 125.9, 119.9, 118.1, 117.6, 116.5, 80.8, 28.8, 28.3, 26.4; HRMS- ESI calcd for $C_{16}H_{18}O_5NF_3NaS$ 416.0750, found 416.0747 $[M + Na]^+$.

(5-Bromo-2-nitrophenyl)methanol (15). To a stirred solution of 5-bromo-2-nitrobenzaldehyde (14) (1 g, 4.38 mmol) in methanol (20 mL) at 0 °C was added sodium borohydride (162 mg, 4.38 mmol) in portions. Stirring was continued for an additional 15 min at room temperature for complete reaction to take place. Methanol was evaporated from the reaction mixture, the reaction was quenched with cold water, and the mixture was extracted with ethyl acetate (3 × 20 mL). Combined organic layers was washed with brine (20 mL), dried over $NaSO_4$, and filtered. The solvent was evaporated under reduced pressure and purified through flash silica gel column chromatography (30% ethyl acetate in hexanes) to give the required product 15 (1.0 g, quantitative): mp 91–92 °C; IR (neat) ν 3252, 1601, 1518, 1346, 1040, 831, 746 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.97 (s, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.56 (dd, J = 1.9, 8.8 Hz, 1H), 4.90 (s, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 146.8, 141.5, 132.1, 131.7, 129.7, 127.2, 61.3; HRMS-APCI calcd for $C_7H_6O_3NBr$ 230.9525, found 230.9525 $[M]^+$.

((5-Bromo-2-nitrobenzyl)oxy)-tert-butyldimethylsilane (16). To a stirred solution of (5-bromo-2-nitrophenyl)methanol (15) (1 g, 4.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added imidazole (586 mg, 8.62 mmol). After the solution was stirred for 10 min, tert- butyldimethylsilyl chloride (969 mg, 6.46 mmol) was added. The temperature was raised to 25 °C, and stirring was continued for an additional 12 h at room temperature. After completion of reaction, water (20 mL) was added to reaction mixture. The organic layer was separated, washed with brine (20 mL), dried over Na_2SO_4, and filtered. Solvent was evaporated under reduced pressure and purified through flash silica gel column chromatography (5% ethyl acetate in hexanes) to give the required product 16 (1.35 g, 90%): mp 38−40 °C; IR (neat) ν 2955, 2857, 1604, 1566, 1343, 1109, 837, 779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 5.08 (s, 2H), 0.98 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 140.5, 131.3, 130.6, 129.4, 126.1, 61.8, 25.9, 18.3, −5.4; HRMS-APCI calcd for $C_{13}H_{21}O_3NBrSi$ 346.0468, found 346.0472 $[M + H]^+$.

tert-Butyl((5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-nitro- benzyl)-oxy)dimethylsilane (8). A mixture of ((5-bromo-2- nitrobenzyl)oxy)(tert-butyl)dimethylsilane 16 (1.2 g, 3.47 mmol), potassium acetate (1.02 g, 10.4 mmol), Pd(dppf) Cl_2 (142 mg, 0.17 mmol)and bis(neopentyl glycolate)diboron (1.18 g, 5.2 mmol) in acetonitrile (20 mL) was heated at reflux under nitrogen atmosphere for 1 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL) and filtered with Celite. The filtrate was concentrated under reduced pressure and purified through silica gel column chromatography (10% ethyl acetate in hexanes) to afford required compound 8 (1.18 g, 90%). m.p: 40−41 °C; IR (neat) ν 2958, 2857, 1520, 1479, 1335, 1255, 1130, 838, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 5.08 (s, 2H), 3.79 (s, 4H), 1.03 (s, 6H), 0.97 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 136.3, 133.9, 132.9, 123.3, 62.3, 31.9, 25.9, 21.8, 18.4, −5.4; HRMS-APCI calcd for $C_{18}H_{31}O_5NBSi$: 380.2059, found 380.2065 $[M + H]^+$.

tert-Butyl (6-(3-(((tert-Butyldimethylsilyl)oxy)methyl)-4-ni- trophenyl)-7,8-dihydronaphthalen-2-yl)carbamate (17). A mag- netically stirred solution of 6-((tert-butoxycarbonyl)amino)-3,4-dihy- dronaphthalen-2-yl trifluoro-methanesulfonate (7) (1 g, 2.54 mmol) in THF/H_2O (60 mL) (9:1) was mixed with tert-butyl((5-(5,5-dimethyl- 1,3,2-dioxaborinan-2-yl)-2-nitrobenzyl)-oxy)dimethylsilane (1 g, 2.63 mmol), triethylamine (3.5 mL, 25.3 mmol), and Pd(dppf)Cl_2 (207 mg, 0.25 mmol). The reaction was run under nitrogen atmosphere with refluxing for 1 h. The cooled reaction mixture was diluted with ethyl acetate (100 mL), washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, and filtered, and solvent was evaporated under reduced pressure and purified through silica gel column chromatography (10% ethyl acetate in hexanes) to afford target compound 17 (1.1 g, 85%): mp 123−125 °C; IR (neat) ν 3350, 2930, 1730, 1574, 1516, 1332, 1252, 1106, 836, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.7 Hz, 1H), 8.09−8.06 (m, 1H), 7.52 (dd, J = 8.4, 2.0 Hz, 1H), 7.35 (s, 1H), 7.12−7.06 (m, 2H), 6.99 (s, 1H), 6.53 (s, 1H), 5.15 (s, 2H), 2.96 (t, J = 8.5 Hz, 2H), 2.75 (t, J = 8.5 Hz, 2H), 1.53 (s, 9H), 1.00 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 146.8, 144.4, 138.9, 138.1, 136.4, 135.0, 129.2, 127.9, 127.4, 125.2, 123.8, 123.3, 117.4, 116.4, 80.7, 62.3, 28.3, 28.2, 25.9, 25.8, 18.3, −5.4; HRMS-ESI calcd for $C_{28}H_{38}O_5N_2NaSi$ 533.2442, found 533.2438 $[M + Na]^+$.

(5-(6-Amino-3,4-dihydronaphthalen-2-yl)-2-nitrophenyl)- methanol (6). To a stirred solution of tert-butyl (6-(3-(((tert- butyldimethylsilyl)oxy)methyl)-4-nitrophenyl)-7,8-dihydronaphtha- len-2-yl)carbamate (17) (1 g, 1.96 mmol) in THF (40 mL) was added slowly TFA (10 mL) at 0 °C. Subsequently, the temperature was raised to 25 °C and stirring was continued for an additional 1 h. After completion of the reaction, the reaction mixture was evaporated, quenched with saturated aqueous $NaHCO_3$ (10 mL), and extracted with ethyl acetate (3 × 20 mL), the combined organic layers were dried over Na_2SO_4 and filtered, and solvent was evaporated under reduced pressure and purified through silica gel column chromatog- raphy (5% methanol in chloroform) to afford target compound 6 (550 mg, 95%): mp 138–140 °C; IR (KBr): ν 3389, 3276, 2931, 1599, 1497, 1214, 1082, 878, 832, 755 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6)δ8.05(d,J=8.7Hz,1H),7.95(s,1H),7.61(d,J=8.2Hz,1H), 7.08 (s, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 6.44–6.38 (m, 2H), 5.56 (t, J = 5.6 Hz, 1H), 5.38 (s, 2H), 4.88 (d, J = 5.5 Hz, 2H), 2.77(t,J=8.4Hz,2H),2.63(t,J=8.4Hz,2H);^{13}CNMR(125 MHz, DMSO-d_6) δ 149.3, 146.4, 143.9, 139.2, 136.4, 129.6, 128.9, 128.4, 128.3, 123.2, 122.9, 122.3, 112.8, 111.6, 60.3, 28.0, 25.1; HRMS- ESI calcd for $C_{17}H_{16}O_3N_2Na$ 319.1053, found 319.1057 $[M + Na]^+$.

(5-(6-(Bis(2-(2-(2-methoxyethoxy)ethoxy)ethyl)amino)-3,4- dihydronaphthalen-2-yl)-2-nitrophenyl)methanol (18). To an anhydrous acetonitrile (8.0 mL) solution of (5-(6-amino-3,4-dihydronaphthalen-2-yl)-2-nitrophenyl)methanol (6) (204 mg, 0.68 mmol), sodium iodide (1 g, 6.6 mmol), and N-ethyldiisopropylamine (436 mg, 3.37 mmol) was added 1-bromo-2-(2-(2-methoxyethoxy)- ethoxy)ethane (760 mg, 3.34 mmol). The reaction mixture was heated under reflux for 5 days. After the mixture was cooled to room temperature, white solids were filtered. The filtrate was washed with water, dried over Na_2SO_4, and purified through silica gel column chromatography (100% ethyl acetate) to afford required compound 18 (303 mg, 75%): IR (neat) ν 3435, 2821, 1595, 1511, 1328, 1213, 1086, 1030, 835, 799 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 8.13 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 1.9 Hz, 1H), 7.54 (dd, J = 8.8, 2.1 Hz, 1H), 7.04 (d, J = 9.0 Hz, 1H), 6.57–6.53 (m, 2H), 5.00 (d, J = 3.3, 2H), 3.69– 3.59 (m, 20H), 3.57–3.53 (m, 4H), 3.38 (s, 6H), 2.92 (t, J = 8.5 Hz, 2H), 2.73 (t, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, CD_3CN) δ 149.2, 148.0, 145.5, 139.7, 138.0, 129.9, 129.0, 126.2, 124.6, 124.0, 118.3, 111.8, 110.6, 72.6, 71.4, 71.2, 71.1, 69.3, 62.2, 58.9, 51.6, 29.5, 26.5; HRMS-ESI calcd for $C_{31}H_{44}O_9N_2Na$ 611.2939, found 611.2934 $[M + Na]^+$.

(S)-5-(5-(6-(Bis(2-(2-(2-Methoxyethoxy)ethoxy)ethyl)amino)- 3,4-dihydronaphthalen-2-yl)-2-nitrobenzyl) 1-tert-Butyl 2- ((tert-butoxycarbonyl)amino)pentanedioate (20). To a solution of (5-(6-(bis(2-(2-(2-methoxyethoxy)ethoxy)ethyl)amino)-3,4-dihy- dronaphthalen-2-yl)-2-nitrophenyl)methanol (18) (110 mg, 0.18 mmol) in DCM (2 mL) were added (S)-5-tert-butoxy-4-((tert- butoxycarbonyl)amino)-5-oxopentanoic acid (113 mg, 0.37 mmol), EDC (53.8 mg, 0.28 mmol), and DMAP (2.2 mg, 0.018 mmol). The reaction was allowed to stir for 20 h for complete reaction. The reaction was diluted with CH_2Cl_2 (5 mL), washed with 1 M HCl, saturated $NaHCO_3$ solution, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (100% ethyl acetate) to provide required compound 20 (147 mg, 90%): IR (neat) ν 3336, 2876, 1738, 1598, 1472, 1393, 1213, 1149, 932, 847, 798 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 8.08 (dd, J = 8.8, 2.4 Hz, 1H), 7.73 (s, 1H), 7.62 (d, J = 9.1 Hz, 1H), 7.07 (s, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.59 (s, 1H), 6.55 (d, J = 8.5 Hz, 1H), 5.55 (d, J = 7.8 Hz,

1H), 5.47 (s, 2H), 4.07–3.98 (m, 1H), 3.63– 3.52 (m, 20H), 3.45 (t, J = 4.2, 4H), 3.28 (s, 6H), 2.87 (t, J = 8.2, 2H), 2.68 (t, J = 8.2, 2H), 2.50 (t, J = 7.5 Hz, 2H), 2.14–2.04 (m, 1H), 1.93–1.85 (m, 1H), 1.42 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN) δ 173.2, 149.4, 148.2, 145.9, 138.0, 133.5, 131.3, 130.0, 129.6, 129.5, 126.6, 125.4, 125.1, 123.5, 118.3, 111.8, 110.6, 82.3, 79.9, 72.6, 73.4, 71.2, 71.1, 69.3, 64.2, 58.9, 51.6, 31.1, 29.5, 28.5, 28.1, 27.8, 26.4; HRMS-ESI calcd for $C_{45}H_{67}O_{14}N_3Na$ 896.4515, found 896.4490 $[M + Na]^+$.

(S)-2-Amino-5-((5-(6-(bis(2-(2-(2-methoxyethoxy)ethoxy)- ethyl)amino)-3,4-dihydronaphthalen-2-yl)-2-nitrobenzyl)oxy)- 5-oxopentanoic Acid (4). To a stirred solution of (S)-5-(5-(6- (bis(2-(2-(2-ethoxyethoxy)ethoxy)ethyl)amino)-3,4-dihydronaphtha- len-2-yl)-2-nitrobenzyl) 1-tert-butyl 2-((tert-butoxycarbonyl)amino)- pentanedioate 20 (25 mg, 0.028 mmol) in anhydrous CH_2Cl_2 (1 mL) was added trifluoroacetic acid (0.25 mL). After 5 h at room temperature under nitrogen atmosphere the solution was evaporated to yield caged glutamate 4 (20 mg, quantitative yield): IR (neat) ν3445, 2891, 2608, 196, 1784, 1696, 1514, 1333, 1131, 764, 594 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d) δ 8.32 (s, 3H), 8.11 (d, J = 8.2 Hz, 1H), 7.77 (s, 1H), 7.74 (dd, J = 8.8, 1.9 Hz, 1H), 7.17 (s, 1H), 7.08 (d, J = 8.5 Hz, 1H), 6.59 (s, 1H), 6.54 (dd, J = 8.4, 2.1 Hz, 1H), 5.47 (s, 2H), 3.98 (s, 1H), 3.60–3.46 (m, 20H), 3.41 (t, J = 4.1, 4H), 3.23 (s, 6H), 2.85 (t, J = 8.2, 2H), 2.66 (t, J = 8.2, 2H), 2.71–2.53 (m, 2H), 2.18–2.00 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d) δ 171.33, 147.93, 146.43, 144.67, 136.57, 131.68, 129.53, 128.96, 128.50, 125.59, 125.15, 124.41, 122.03, 110.47, 109.36, 71.24, 69.93, 69.80, 69.61, 67.90, 63.21, 57.99, 50.21, 29.14, 28.18, 27.40, 25.17, 24.94; HRMS- ESI calcd for $C_{36}H_{52}O_{12}N_3$ 718.3546, found 718.3545 $[M + H]^+$.

tert-Butyl 2,2′-(6-(3-(Hydroxymethyl)-4-nitrophenyl)-7,8-di- hydronaphthalen-2-ylazanediyl)diacetate (19). To an anhydrous acetonitrile (2.0 mL) solution of (5-(6-amino-3,4-dihydronaphthalen- 2-yl)-2-nitrophenyl)methanol (6)(25 mg, 0.084 mmol), sodium iodide (126.5 mg, 0.84 mmol), and N-ethyldiisopropylamine (54.6 mg, 0.42 mmol) was added tert-butyl bromoacetate (164 mg, 0.84 mmol). The reaction mixture was heated under reflux for 24 h. After the mixture was cooled to room temperature, solvent was evaporated and diluted with CH_2Cl_2, and white solids were filtered. Filtrate was concentrated in vacuo and purified through silica gel column chromatography (20% ethyl acetate in hexanes) to afford required compound 19 (35 mg, 80%): IR (neat) ν 2978, 1734, 1597, 1510, 1456, 1330, 1213, 1149, 1085, 842, 622 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.8, 2.5 Hz, 1H), 7.75 (d, J = 1.9 Hz, 1H), 7.51 (td, J = 8.5, 2.4 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.97 (s, 1H), 6.42– 6.40 (m, 1H), 6.39 (s, 1H), 4.97 (s, 2H), 4.01 (s, 4H), 2.89 (t, J = 8.0 Hz, 2H), 2.64 (t, J = 8.0 Hz, 2H), 1.47 (s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 148.2, 147.6, 145.0, 137.3, 136.7, 13.7, 128.7, 128.4, 125.7, 125.5, 124.5, 123.9, 111.5, 110.2, 81.9, 63.8, 54.5, 28.8, 28.1, 25.8; HRMS-ESI calcd for $C_{29}H_{36}O_7N_2Na$ 547.2414, found 547.2409 $[M + Na]^+$.

(S)-5-(5-(6-(Bis(2-tert-butoxy-2-oxoethyl)amino)-3,4-dihy- dronaphthalen-2-yl)-2-nitrobenzyl) 1-tert-Butyl 2-(tert- Butoxycarbonylamino)pentanedioate (21). To a solution of tert-butyl 2,2′-(6-(3-(hydroxymethyl)-4-nitrophenyl)-7,8-dihydronaph- thalen-2-ylazanediyl)diacetate (19) (34 mg, 0.064 mmol) in DCM (2 mL) was added (S)-5-tert-butoxy-4-((tert-butoxycarbonyl)amino)-5-oxopentanoic acid (22) (39 mg, 0.129 mmol), EDC (18.6 mg, 0.097 mmol), and DMAP (0.8 mg, 0.0064 mmol). The reaction was allowed to stir for 12 h for complete reaction. The reaction was diluted with CH_2Cl_2 (5 mL), washed with 1 M HCl, saturated $NaHCO_3$ solution, and brine, dried

over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexanes) to provide required compound 21 (42 mg, 80%): IR (neat) ν 2979, 2930, 1741, 1600, 1577, 1506, 1457, 1333, 1216, 1152, 843, 797 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.5 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 8.6, 2.0 Hz, 1H), 7.05 (d, J = 9.1 Hz, 1H), 6.95 (s, 1H), 6.43–6.41 (m, 1H), 6.40 (s, 1H), 5.54 (s, 1H), 5.09 (d, J = 7.6 Hz, 1H), 4.27–4.17 (m, 1H), 4.03 (s, 4H), 2.90 (t, J = 7.7, 2H), 2.70 (t, J = 7.7 Hz, 6H), 2.60–2.41 (m, 2H), 2.27– 2.15 (m, 1H), 2.01–1.90 (m, 1H), 1.47 (s, 18H), 1.45 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 171.2, 169.9, 155.4, 148.2, 147.3, 145.0, 136.6, 132.2, 131.5, 128.8, 128.4, 125.7, 124.9, 124.4, 124.3, 111.4, 110.2, 82.3, 81.8, 63.6, 54.5, 53.3, 30.2, 28.8, 28.3, 28.1, 27.9, 25.8; HRMS-ESI calcd for $C_{43}H_{59}O_{12}N_3Na$ 832.3991, found 832.3994 $[M + Na]^+$.

(S)-2,2′-(6-(3-((4-Amino-4-carboxybutanoyloxy)methyl)-4- nitrophenyl)-7,8-dihydronaphthalen-2-ylazanediyl)diacetic Acid (5). To a stirred solution of (S)-5-(5-(6-(bis(2-tert-butoxy-2-oxoethyl)amino)-3,4-dihydronaphthalen-2-yl)-2-nitrobenzyl) 1-tert- butyl 2-(tert-butoxycarbonylamino)pentanedioate (21) (40 mg, 0.049 mmol) in anhydrous CH_2Cl_2 (3 mL) was added trifluoroacetic acid (1.0 mL). After 5 h at room temperature under nitrogen atmosphere, the solution was evaporated to yield caged glutamate 5 (32 mg, quantitative yield): IR (neat) ν 3437, 2935, 2633, 1734, 1601, 1510, 1331, 1190, 1139, 1080, 842 cm^{-1}; ^1H NMR (400 MHz, DMSO-d) δ 8.24 (s, 3H), 8.05 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 13.0 Hz, 1H), 7.12 (s, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.36 (s, 1H), 6.31 (d, J = 7.7 Hz, 1H), 5.40 (s, 2H), 4.07 (s, 4H), 3.95–3.86 (m, 1H), 2.78 (t, J = 7.7Hz, 2H), 2.60 (t, J = 7.7, 2H), 2.56–2.46 (m, 2H), 2.11–1.89 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d) δ 172.5, 171.8, 171.0, 148.6, 146.7, 145.3, 136.8, 132.2, 130.9, 129.2, 128.7, 126.1, 125.7, 125.0, 123.7, 111.1, 110.0, 63.6, 56.4, 53.3, 29.6, 28.5, 25.6, 25.4; HRMS-ESI calcd for $C_{26}H_{28}O_{10}N_3$ 542.1769, found 542.1765 $[M + H]^+$.

tert-Butyl (6-(4-Nitrophenyl)-7,8-dihydronaphthalen-2-yl)- carbamate (23). 6-((tert-Butoxycarbonyl)amino)-3,4-dihydronaph- thalen-2-yl trifluoromethanesulfonate 7 (200 mg, 0.5 mmol), 4- nitrobenzeneboronic acid (170 mg, 1.0 mmol), cesium carbonate (829 mg, 2.5 mmol), and $Pd(PPh_3)_4$ (58.8 mg, 0.05 mmol) were mixed in 1,4-dioxane (10 mL) and H_2O (2.0 mL) in a round-bottom flask. The mixture was heated at 100 °C for 12 h and then partitioned between H_2O and EtOAc. The insoluble solid was filtered, and the organic layer was concentrated in vacuo and purified through column chromatog- raphy to afford the desired product 23 (170 mg, 91%): mp 153–155 °C; IR (neat) ν 3361, 2979, 1724, 1514, 1233, 1157, 852, 750 cm^{-1}; ^1HNMR(500MHz,$CDCl_3$)δ8.20(d,J=8.8Hz,2H),7.63(d,J= 8.9 Hz, 2H), 7.35 (s, 1H), 7.10 (s, 1H), 6.96 (s, 1H), 6.54 (s, 1H), 2.95 (t, J = 8.1, 2H), 2.73 (t, J = 8.1, 2H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 147.8, 146.5, 138.4, 136.5, 134.7, 129.1, 128.2, 127.8, 125.4, 124.0, 117.5, 116.6, 80.9, 28.5, 28.3, 26.1; HRMS-ESI calcd for $C_{21}H_{22}O_4N_2Na$ 389.1471, found 389.1473 $[M + Na]^+$.

ASSOCIATED CONTENT

Supporting Information^1H and ^{13}C spectra of new compounds 4–8, 11, 12, 15–21, and 23. UV and emission spectra of compounds 20 and 21. Computational details, optimized

geometries, excited-state structures, and natural transition orbitals. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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